REMARKS

With entry of the instant amendment, claims 1 and 5 have been amended, claims 6-16 have been cancelled, and new claims 17-19 have been added. Claims 1-5, and 17-19 are therefore pending and under examination.

Cancellation of claims 6-16 is without prejudice to subsequent revival of the claimed subject matter in a divisional application.

The amendments to the claims add no new matter and are supported throughout the application as filed.

Claim 1 has been amended to recite aligning a set of at least two parent protein have 60% or greater amino acid similarity and at least one common biological activity; and selecting sites in the parent proteins that are mismatched. Support can be found, *e.g.*, on page 14, paragraph 62 bridging to page 17, paragraph 72.

Claim 1 has also been amended to recite that the library is created by introducing a degenerate codon at at least five mismatched positions where the degenerate codon alternatively encodes at least two parent amino acid residues at each of the five mismatched positions, and wherein the parental codon that occurs at each of the five mismatched positions is independent of the parental codon that occurs at the other of the five mismatched sites. Support can be found, *e.g.*, on page 3, paragraph 13, lines 1-4; on page 12, paragraph 57, lines 1-3; page 17, paragraph 74; page 18, paragraphs 76 and 77;

New claims 17 and 18 add no new matter and are supported by the application as filed, *e.g.*, in Example 2.

New claim 19 recites that at least twenty mismatched positions are selected. Support can be found, *e.g.*, on page 12, lines 1-3 of paragraph 57.

For convenience, the objections/rejections are addressed in the order presented in the Office Action mailed October 11, 2005.

Objections to the abstract

The Examiner alleges that the abstract was not proper. The abstract has been amended to more precisely reflect the invention. Applicants therefore respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 5 was rejected as allegedly indefinite for insufficient antecedent basis for the term "the wild-type proteins". The claim has been amended to provide proper antecedent basis. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 1-3 and 5 were rejected as allegedly unpatentable over Christians *et al.*, (*Nature Biotechnol.* 17:259-264, 1999) in view of any one of, or combination of, Farinas *et al.*, *Curr. Opin. in Biotechnol.* 12: 545-551, 2001; Gibbs *et al.*, *Gene* 271:13-20 (2001) and Joern *et al.*, *J. Mol. Biol.* 316:643-656, 2002. Christians *et al.* is cited for teaching a method for creating hybrid proteins having a common biological activity by family shuffling. Although Christians *et al.* does not explicitly teach that the majority of the library members have a greater than 60% amino acid similarity to any of the parent proteins, the Examiner sites Farinas *et al.*, Gibbs *et al.*, and Joern *et al.* as providing evidence that one of skill in the art would have recognized the advantages of using sequences with either of 60% or 80% amino acid similarity between the two parent proteins, and 60% or 80% amino acid similarity between a majority of the library members and any parent protein. The Examiner contends that Christians *et al.* in combination with any of the three cited secondary references render the invention *prima facie* obvious, as one of skill in the art performing directed evolution would have recognized the advantages of using sequences having either 60% or 80% similarity between the majority of the library members and parent proteins. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse.

The libraries of the claimed methods and those in the cited art have different characteristics

The instant invention is a method of generating hybrid proteins where the method comprises determining mismatched sites of parent molecules that are structurally similar and have the same biological function. After the amino acid sequence of the homologous parent proteins are aligned, the amino acid residues that are different between the sequences are identified. A minimal encoding sequence is derived by identifying codons that will encode both (assuming for the sake of this example that there are only two parents) parental amino acid residues at the mismatched site with a minimal number of degeneracies, *i.e.,* positions at which alternative nucleotides can be incorporated, resulting in different amino acid residues at the position encoded by the codon. The result is a population of hybrid proteins that are produced in which, at a give position, some protein sequences will have the residue from one parent at a selected mismatched site and others will have the residue from the other parent. For a given hybrid sequence, the amino acid residue that occurs at one mismatched position is independent of the amino acid residue that occurs at a second mismatched position, thus often resulting in stretches of amino acid sequences in a typical hybrid protein library member that have alternating parental residues at consecutive mismatched sites.

In Christians *et al.*, the shuffling libraries were different. First, although sequences may have been compared to determine the degree of similarity, particular mismatched positions were not selected. The initial library was generated by recombining randomly DNAse I-digested fragments in a primer-less polymerase reaction (*see, e.g.,*) page 263, Experimental Protocol. Colonies were then screened to identify those that conferred AZT sensitivity. Confirmed clones were then mixed together to provide the genetic material for the next cycle of shuffling and screening. Thus, there was no selection of mismatched positions.

Further, the occurrence of the particular parental residues at mismatched sites in stretches of amino acid sequences was not independent in the sequence comparison in Figure 2 that was cited by the Examiner. Simple inspection of the sequences in Figure 2 shows that residues from one of the parent proteins occur in blocks. For example, the C3 and C4 proteins at

positions 260 through 290 have residues from only one parent, TK1, rather residues from both TK1 and TK2.

In summary, Christians *et al.* fails to teach or suggest the elements of the claimed invention. Accordingly, the claims are unobvious over the cited art.

Claims 1-5 were rejected as allegedly unpatentable over Christians *et al.*, Farinas *et al.*, Gibbs *et al.* and/or Joern *et al.*, as applied above, and further in view of Xia *et al.* To the extent that the rejection applies to the amended claims, Applicants respectfully traverse. The primary references fail to teach or suggest the elements of the claimed invention. Xia *et al.* provides no teachings that overcome the deficiencies of the primary references. Claims 1-5 are therefore patentable over the combination of references.

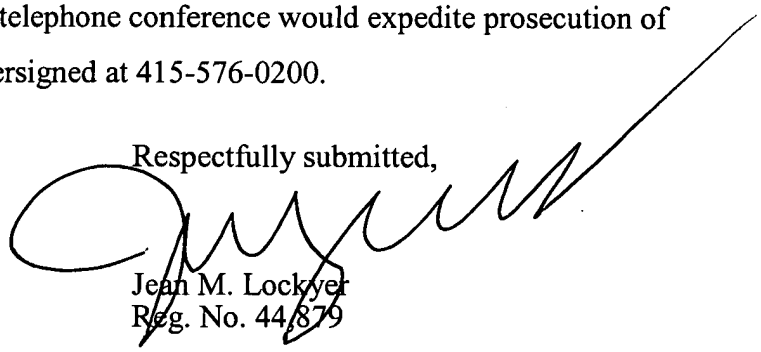
In view of the foregoing, Applicants respectfully request withdrawal of the rejections.

CONCLUSION

Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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